# A key role of C5a/C5aR activation for the development of sepsis

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**Abstract: In recent studies, evidence has been provided for complement activation early during the onset of experimental sepsis. Excessive production of the anaphylatoxin C5a thereby appears to elicit various harmful effects. Blockade of C5a or C5a receptor (C5aR) at the start of experimental sepsis has been demonstrated to greatly improve survival in rodents. There is evidence that C5a, during the onset of sepsis, enhances the production of various proinflammatory mediators in different cell types. Besides its known, other proinflammatory effects, recent work suggested an inhibitory role of C5a for innate-immune functions of phagocytic cells (phagocytosis, reactive oxygen species production, chemotaxis) during experimental sepsis. This review article provides an overview of the important role of C5a/C5aR activation for the onset and development of sepsis. *J. Leukoc. Biol.* 74: 966–970; 2003.**

***Key Words:*** *inflammation · complement · cytokines · LPS · innate immunity · antibody*

## INTRODUCTION

The complement system represents a powerful key player of humoral defense against invading microorganisms. The complement system uses a variety of serum proteins, which interact in a cascade of activation steps. The ultimate, direct function of complement activation in the context of humoral defense is production of mediators that are proinflammatory and promote the phagocytosis as well as the formation of pores in the bacteria leading to their lysis. This goal can be reached by different pathways of complement activation, depending on the type of trigger of activation.

The classical pathway is activated by antigen-antibody complexes and requires all nine complement proteins. The lectin pathway of complement activation is initiated by bacterial surface sugars (mannose) via the mannose-binding lectin (MBL) protein in serum and subsequent interaction with MBL-activated serine proteases. Thereafter, this pathway functions identically to the classical pathway, using C2 and C4 for following cleavage of C3. The alternative complement pathway is activated by bacterial lipopolysaccharide (LPS) and by related products. All complement activation pathways converge at the level of C3 and lead to the cleavage products, C3a and C5a, as well as the terminal membrane attack complex, C5b-9, which forms pores in the membrane of bacteria and cells, ultimately causing their lysis. Despite this beneficial effect of complement activation for the humoral defense, the recent works have underscored a variety of harmful effects associated with activation of the complement system.

On top of the list of potentially harmful mediators is the complement anaphylatoxin C5a. This 74 amino acid-containing protein was originally found to have strong chemotactic effects on neutrophils [1]. Many proinflammatory effects were discovered, such as release of granular enzymes from phagocytic cells [2], production by neutrophils of superoxide anion [3], vasodilatation together with increased vascular permeability [4], and induction of thymocyte apoptosis during sepsis [5, 6].

The corresponding seven transmembrane-spanning, G-protein-coupled receptor C5aR was cloned in 1991 [7] and has since been discovered to play an important role for a variety of inflammatory diseases such as the reverse-passive arthus reaction [8] and ischemia reperfusion [9]. The complexity of C5a/C5aR-induced effects on different immune functions and systems is reflected by the fact that blockade of C5a or C5aR has been suggested to be beneficial in a variety of inflammatory disorders. Recently, blockade of C5a was demonstrated to be beneficial in cecal ligation and puncture (CLP)-induced polymicrobial sepsis [10]. Since then, there has been accumulating evidence for a key role of C5a/C5aR activation for the development and during the onset of sepsis. This key role of C5a/C5aR activation will be the focus of this manuscript.

## EVIDENCE FOR IMPORTANCE OF C5a DURING SEPSIS

Earlier studies have suggested that complement activation during human sepsis, especially as reflected in elevated levels of C5a, is associated with significantly reduced survival rates together with multi-organ failure when compared with less-severe septic patients and survivors [11–13]. Experimental studies in monkeys suggested that blockade of C5a by antibodies could significantly attenuate *Escherichia coli*-induced septic shock and adult respiratory distress syndrome [14, 15], and studies in rats suggested that LPS-induced septic shock

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could be mimicked by injection of C5a, and blockade of C5a via antibody attenuated LPS-induced responses [16].

Blockade of C5a during experimental sepsis (CLP) was recently found to be protective in rats [10]. In this study, antibodies to C5a were administered at the start of CLP and showed significant improvement in terms of survival of septic rats. Follow-up studies aimed to determine the efficacy of blocking different regions of C5a by antibodies revealed that blockade of the middle or C-terminal region of C5a was an effective strategy in terms of improving survival in CLP rats [17]. Also, it was demonstrated that delayed infusion (6 and 12 h after CLP) of antibodies to C5a still resulted in significant survival benefits for the animals. C5a blockade during sepsis also greatly reduced appearance of multi-organ failure in rats [18].

Besides the activation of complement in the plasma during sepsis or after LPS infusion, recent work demonstrated that certain cells (e.g., alveolar macrophages) and neutrophils, when activated, are capable of cleaving C5 to generate C5a, suggesting that C5a generation in compartments such as the lung could be regulated independent of complement proteins that form C5 convertases (C5-cleaving activities) [19].

## C5aR IN SEPSIS

Soon after the findings in sepsis, which demonstrated benefits of blockade of C5a with antibodies, C5aR became one focus of interest. Blockade of C5aR by a small cyclic C5aR antagonist as well as by antibodies to the N-terminal end of C5aR resulted in significantly improved survival in CLP mice [5, 20]. C5aR was originally believed to be present only in myeloid cells, but it has since been found to be present in a broad variety of cell types such as alveolar and bronchiolar epithelial cells [21, 22] and endothelial cells [23–25]. It is interesting that a strong increase in C5aR surface expression was found early (6 h) after CLP in mouse lung, liver, kidney, and heart [5]. This increase was found to be strongly dependent on plasma interleukin (IL)-6, as IL-6 blockade in CLP mice inhibited the C5aR increase in all four organs and resulted in improved survival in a dose-dependent manner [26]. C5aR blockade with antibodies, in turn, resulted in decreased IL-6 plasma levels at 6 h after sepsis [5]. These data suggest a complex interaction and positive feedback between IL-6 generation and C5aR up-regulation and between C5aR activation (via C5a) and IL-6 production. As C5a is believed to be activated within the first few hours of CLP-induced sepsis in rodents (and IL-6 levels are peaking at ~6 h), it is tempting to hypothesize that the early C5a generation may be the driving force for up-regulation of IL-6. Earlier findings in alveolar epithelial cells demonstrated that LPS-induced generation of mediators, such as tumor necrosis factor α (TNF-α) and chemokines (macrophage-inflammatory protein-2, cytokine-induced neutrophil chemoattractant), were strongly enhanced in the copresence of C5a. In vitro data from our group indicate that C5a may also enhance LPS-induced IL-6 production in granulocytes [27]. The same has been suggested for peripheral blood mononuclear cells (PBMC) [28]. In such a scenario, early C5a generation during sepsis would boost mediator-induced production of IL-6 in the serum, resulting in fast up-regulation of C5aR in various organs, which in turn, could make these organs more susceptible to C5a effects but also result in reducing circulating C5a levels by binding and internalizing C5a as a potential negative feedback (**Fig. 1**). Increased C5aR gene expression was also found during various human kidney diseases [29]. The effect, however, of C5aR increase and activation in the various organs is unclear so far.

In contrast to organs, there is evidence that C5aR expression in neutrophils may be regulated differently during sepsis, as binding of radiolabeled C5a to PMN has been demonstrated to be vastly down-regulated during CLP-induced sepsis in rodents [18], which was reversed by blockade of C5a with antibodies. The loss of C5aR on blood neutrophils appears to be a result of internalization of C5aR–C5a complexes (R-F. Guo, N. C. Riedemann et al., submitted). An earlier study suggested similar findings in a model of LPS infusion in rabbits [30]. Recently, in humans with sepsis, C5aR expression on granulocytes was also described to be down-regulated [31]. Data from our group suggest that C5aR expression in PMN during experimental sepsis may be an indicator for outcome and therefore, may have potential for prognostic use in the clinic (R-F. Guo, N. C. Riedemann et al., submitted).

## C5a EFFECTS ON CYTOKINE PRODUCTION IN VITRO

In vitro results with C5a stimulation of various cell types did not result in significant mediator generation in most cases. As mentioned earlier, when alveolar epithelial cells were costimulated with LPS and C5a, a much higher production of TNF-α and chemokines could be observed when compared with cells stimulated only with LPS [32], suggesting a strong, stimulatory role of C5a for the mediator-induced production of various proinflammatory cytokines. Earlier studies in PBMC had demonstrated that C5a stimulation resulted in gene transcription (but not translation) for IL-1β, as significant increases in protein expression for IL-1β could not be detected [33, 34]. Another study demonstrated that prestimulation of granulocytes with C5a or other chemoattractants resulted in significantly reduced LPS-induced IL-8 production, and costimulation with C5a and LPS resulted in a synergistic increase of IL-8 production as compared with LPS-only-stimulated granulocytes [35]. In the case of LPS-induced production of the proinflammatory cytokine IL-6 by PBMC, similar findings have been made when they were costimulated with C5a and LPS [28]. Recent findings of our group suggest that this could be true in granulocytes as well and may have systemic implications during CLP-induced sepsis (N. C. Riedemann, R-F. Guo et al., manuscript submitted).

Another in vitro study found that C5a strongly reduced mediator (LPS, interferon-γ)-induced production of IL-12 in human monocytes [36]. We recently presented evidence that LPS-induced TNF-α production was significantly reduced in neutrophils in the copresence of C5a, and the opposite effect (increased TNF-α production) could be seen in macrophages [27]. We interpret these findings to suggest that C5a inhibits the production of an important proinflammatory mediator in

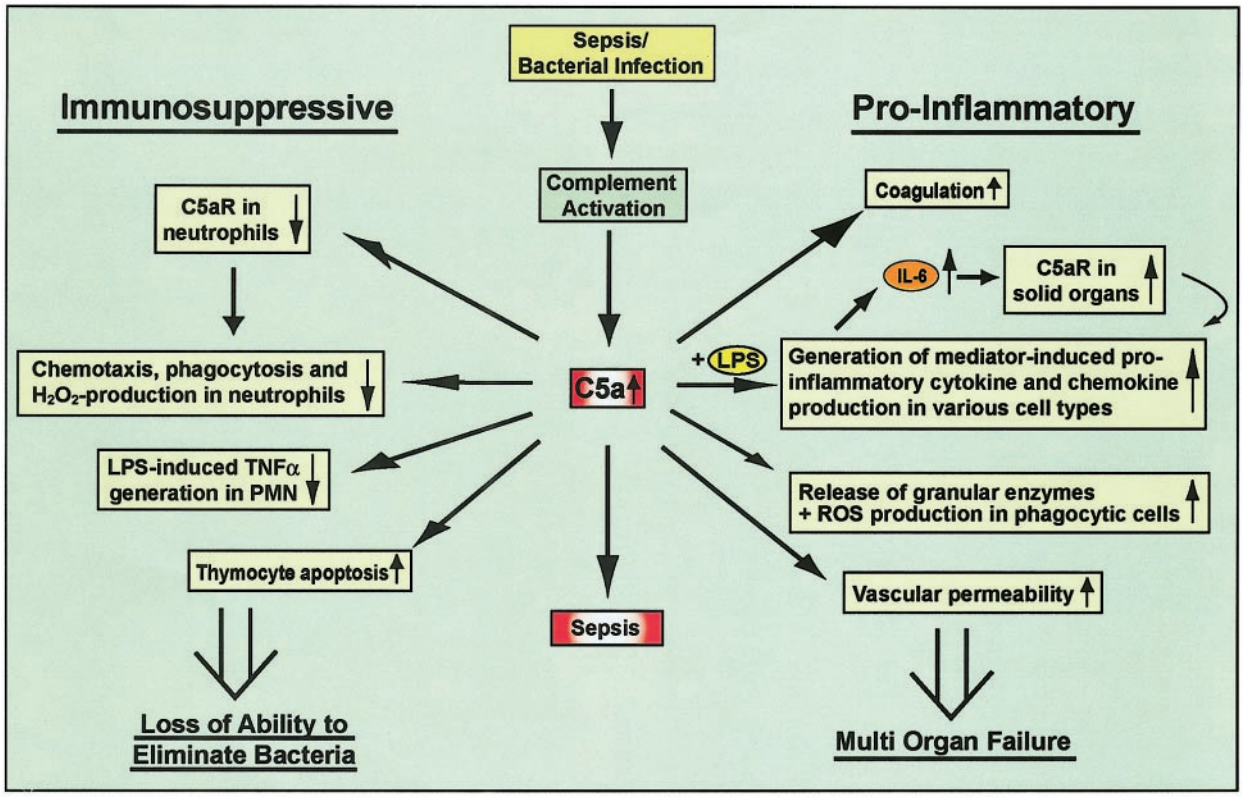


**Fig. 1.** The key role of C5a/C5aR activation for the development of sepsis. Depicted are the proinflammatory and immunosuppressive effects of C5a in the context of sepsis. Rapid complement activation after, e.g., bacterial infection will lead to massive C5a generation at the onset of sepsis, resulting in an overwhelming, proinflammatory response, including production of proinflammatory mediators such as IL-6, which in turn, enhances C5aR expression in various cell types of solid organs, increasing the sensitivity to C5a effects. C5a also enhances vascular permeability, contributing to development of edema, resulting in reduced organ perfusion and oxygen supply. Procoagulatory effects of C5a may promote the development of disseminated intravascular coagulopathy with resulting micro embolisms in various organs. Proinflammatory mediators as well as C5a lead to a massive production of reactive oxygen species (ROS) in phagocytic cells, potentially damaging various organs, resulting in multi-organ failure. Conversely, C5a activation results in inhibition of crucial innate-immune functions of neutrophils, leaving the organism with increased susceptibility to bacterial infection. PMN, Polymorphonuclear leukocytes.

neutrophils, reflecting evidence for a harmful inhibition of innate-immune functions.

In conclusion, C5a, in most of the in vitro experiments, seems to significantly enhance mediator-induced production of cytokines and chemokines with the exception of IL-12 in PBMC and TNF-α in PMN. In the context of sepsis, we believe that a boost of proinflammatory mediator production early during the onset of sepsis may explain the significant contribution of C5a in the onset of sepsis (Fig. 1). For specific cell types (e.g., neutrophils), contact with C5a may result in harmful reduction of certain immune functions, as pointed out below and in Figure 1.

## EVIDENCE FOR HARMFUL EFFECTS OF C5a ON NEUTROPHIL INNATE IMMUNITY

As pointed out in the paragraphs above, neutrophils seem to play a special role in the context of C5a effects during sepsis. IL-6 or LPS does not regulate C5aR in PMN on the transcriptional level, and the surface content on PMN of C5aR has been demonstrated to decrease during sepsis, and an increase was observed of C5aR in lungs, liver, kidney, and heart. Upon contact with C5a, LPS-induced TNF-α production appears to be significantly inhibited by C5a in PMN, and the opposite effect could be observed in macrophages [27].

C5a has been shown to provoke a transient leukocytosis after injection into rabbits [37], supporting the concept that C5a plays an important role for innate immunity via neutrophil recruitment. An earlier study had suggested that exposure of high levels of C5a could lead to nonspecific, chemotactic "deactivation," thereby causing broad neutrophil dysfunction [38]. Our group recently found that blood neutrophils from CLP rats show reduced phagocytosis and defective assembly of reduced nicotinamide adenine dinucleotide phosphate oxidase [39]. Blockade of C5a during sepsis prevented these effects, suggesting a harmful role of C5a for neutrophil innate-immune functions during sepsis. We have also demonstrated that the chemotactic ability in neutrophils was compromised during sepsis as a result of generation of C5a [20]. Recent work extended these findings by demonstrating that the production of ROS in neutrophils is compromised during CLP-induced sepsis in rats related to C5a generation (R-F. Guo, N. C. Riedemann et al., submitted).

A recent study suggested that C5a was also involved in altered neutrophil trafficking during sepsis, as a result of differential regulation of $\beta_1$-integrins [40].

In conclusion, excessive C5a generation during sepsis appears to impair crucial innate-immune functions of neutrophils, leading to a state of "immune paralysis", in which the first line of defense (phagocytosis, $H_2O_2$ production) against invading microorganisms is dysfunctional, leaving the organism susceptible to bacterial infection or superinfection. Obviously, C5a appears to have a central role for the regulation of neutrophil functions during the onset of sepsis. The signaling pathways involved in these C5a effects are as-yet unknown. The underlying molecular mechanisms need to be investigated.

## OTHER HARMFUL EFFECTS OF C5a DURING SEPSIS

Besides the impaired innate-immune functions in neutrophils, other harmful effects of C5a during experimental sepsis have been described. A recent study demonstrated an eminent role of C5a for disordered coagulation and fibrinolysis during sepsis [41]. This study presents the first evidence of a relation between the complement system and coagulation system in a setting of experimental sepsis. Disseminated intravascular coagulopathy occurs frequently in patients with sepsis and contributes to high mortality rates; such findings are of particular interest.

Another recently discovered, potentially harmful role of C5a during sepsis is its ability to induce thymocyte apoptosis under conditions in which C5aR has been up-regulated [6, 42]. Apoptosis of lymphoid cells during sepsis is thought to be related to loss of immune functions during sepsis [43, 44]. In these studies, blockade of C5a during CLP-induced sepsis resulted in potent inhibition of the otherwise observed and earlier described rapid thymus involution during sepsis. Therefore, we hypothesize, that massive C5a generation during the onset of sepsis could lead to a rapid reduction of immunocytes, increasing the susceptibility to infection.

## SUMMARY

Good complement gone bad? Undoubtedly, recent research demonstrates that C5a/C5aR play an important role for the development of sepsis and harmful impairment of crucial innate-immune functions, despite the fact that the complement system is surely one of the most powerful and important defense mechanisms against invading microorganisms. Based on our current understanding, we present the hypothesis that in the context of sepsis, an imbalance of complement activation may be the underlying phenomenon, resulting in excessive C5a generation, leading to the conditions outlined above and depicted in Figure 1.

The effects elicited by C5a/C5aR interaction appear to be organ- and cell-type-specific, and much work needs to be done to define in greater detail the consequences of C5aR activation for a specific cell type and organ, especially on the molecular basis. It is fascinating to observe the broad variety of C5a effects during the onset of sepsis, suggesting C5a to be a key player for the development of sepsis. C5a/C5aR may be interesting targets, especially for preventive treatment of patients at high risk for developing sepsis.

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